

Mechanisms of Immune Privilege in the Eye and Hair Follicle

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It has been recognized for over a century that the eye is endowed with remarkable properties that permit the long-term survival of foreign tumor and tissue grafts that are normally rejected at extraocular sites. This ocular immune privilege was originally attributed to a putative sequestration of antigens in the eye as a result of the conspicuous absence of intraocular lymphatic drainage channels. In the last 30 years, a sizeable body of information indicates that ocular immune privilege is a product of multiple anatomical, physiological, and immunoregulatory processes. Ocular tissues and fluids express a wide variety of anti-inflammatory and immunosuppressive molecules, including CD95L (FasL), transforming growth factor- β , macrophage migration inhibitory factor, α -melanocyte-stimulating hormone, calcitonin gene-related peptide, somatostatin, and complement regulatory proteins. Moreover, antigens entering the anterior chamber of the eye evoke a unique

form of immune deviation that culminates in the antigen-specific suppression of TH1 immune responses. Finally, the intraocular milieu contains both cell membrane and soluble factors that inhibit both the adaptive and innate immune systems. The hair follicle is also recognized for its immune privilege. Like the anterior chamber of the eye, it produces anti-inflammatory and immunosuppressive cytokines, such as transforming growth factor- β and adrenocorticotrophic hormone. The cells of the hair follicle display limited expression of class Ia MHC molecules and, like cells that line the anterior chamber of the eye, are protected against CD8+ cytotoxic T lymphocyte attack. Gaining a better understanding of the immune privilege of the hair follicle may provide insights into the regulation and pathogenesis of immune-mediated diseases of the skin. **Keywords:** Eye/hair follicle/immune privilege. *JID Symposium Proceedings 8:168–172, 2003*

It has been recognized for over a century that the anterior chamber (AC) of the eye is a highly permissive site for the transplantation of tumor and tissue grafts that would otherwise be rejected following transplantation to nonocular sites (Barker, 1977; Head and Billingham, 1985). In the nineteenth century, van Dooremaal (1873) and Zahn (1884) noted the prolonged survival of human tumor cells and fetal cartilage xenografts in the AC of rabbits' eyes. In the 1940s, Greene and Lund (1944) transplanted human tumor cells into the AC of the rabbit eye as a bioassay for determining the malignancy of biopsy specimens. Ten years later, the ground-breaking studies of Medawar firmly established the role of the immune system in organ graft rejection and set the stage for understanding the unique immunological properties of the eye (Medawar, 1945; Medawar, 1948; Billingham *et al*, 1954). The prolonged survival of foreign tissue grafts in the AC of the eye and brain led Medawar to conclude that the AC was endowed with a remarkable immune privilege (Medawar, 1948). The absence of patent lymph vessels draining the interior of the eye led Medawar to conclude that the eye's immune privilege is a consequence of antigen sequestration—a phenomenon that contemporary immunologists would come to know as “immunological ignorance.”

Dynamic Regulatory Processes that Contribute to Immune Privilege It was not for another two decades that this paradigm was re-examined when Kaplan and Streilein injected allogeneic lymphoid cells into the AC of rat eyes and noted that alloantigens introduced into the eye not only were perceived by the systemic immune apparatus but in fact elicited an aberrant immune response that was characterized by an antigen-specific downregulation of cell-mediated alloimmunity and a concomitant activation of humoral antibody responses (Kaplan *et al*, 1975; Kaplan and Streilein, 1977). This deviant form of systemic alloimmunity was termed “lymphocyte-induced immune deviation” (Kaplan and Streilein, 1977). Subsequent investigations by Niederkorn and Streilein demonstrated that the immune deviation induced by AC injection of alloantigens was not a property of the lymphoid cells injected into the AC, but was a stereotypic immune response that was elicited when virtually any antigen was delivered into the AC (Niederkorn *et al*, 1981; Streilein *et al*, 1997). Accordingly, they coined the term “anterior chamber-associated immune deviation” (ACAID) to stress the dynamic nature of the systemic immune response to antigens introduced into the AC and the crucial role of the eye in deviating the immune response down an unconventional pathway (Streilein and Niederkorn, 1981). The ACAID phenotype is characterized by a profound, antigen-specific downregulation of TH1 immune responses, such as delayed-type hypersensitivity (DTH) and a concomitant stimulation of non-complement-fixing IgG1 antibody and cytotoxic T lymphocyte (CTL) responses (Niederkorn, 2002). As a result of the original studies of Kaplan and Streilein (Kaplan *et al*, 1975; Kaplan and Streilein, 1977), ACAID has been demonstrated with a panoply of antigens, including viruses, haptenated cells, soluble proteins,

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Abbreviations: AC, anterior chamber; ACAID, anterior chamber-associated immune deviation; AH, aqueous humor; NK, natural killer (cells).

tumor antigens, and histocompatibility antigens (Nieder Korn, 2002).

Immunoregulatory Factors in the Intraocular Milieu In addition to ACAID, multiple factors contribute to the immune privilege in the AC. The aqueous humor (AH) that fills the AC and bathes the endothelium of the cornea possesses remarkable immunosuppressive and anti-inflammatory properties. Constituents of the AH suppress mitogen- and antigen-driven lymphocyte proliferation *in vitro* (Benezra and Sachs, 1974; Kaiser *et al*, 1989). The AH also suppresses the expression of DTH responses *in situ*. That is, previously activated TH1 cells that produce DTH lesions in the skin fail to produce inflammatory lesions when introduced into the AC (Nieder Korn *et al*, 1990; Cousins *et al*, 1991). At least four different AH-borne factors suppress DTH responses in the eye: (i) TGF- β , (ii) α -melanocyte-stimulating hormone, (iii) vasoactive intestinal peptide, and (iv) calcitonin gene-related peptide (Taylor, 1999). These factors exert other immunological effects that influence immune privilege in the AC. TGF- β_2 , at concentrations found in the AH, alters the behavior of antigen-presenting cells (APC) and downregulates their production of the TH1-inducing cytokine IL-12 while stimulating their synthesis of the TH2 cytokine IL-10 (D'Orazio and Nieder Korn, 1998). Moreover, TGF- β_2 suppresses the activation of T cells and induces APC to present antigen in a manner that culminates in the generation of ACAID rather than in conventional TH1 immune responses (Nieder Korn, 2002). TGF- β_2 also downregulates the expression of class I major histocompatibility complex (MHC) antigens (Ma and Nieder Korn, 1995) and inhibits the cytolytic machinery of natural killer (NK) cells (Rook *et al*, 1986).

Immune privilege in the AC of the eye is also extended to elements of the innate immune system. The single corneal endothelial cell layer that lines the AC expresses little or no detectable class I or II MHC determinants (Nieder Korn, 2002). The absence of conventional class Ia MHC antigens renders corneal endothelial cells highly vulnerable to NK cell-mediated lysis (Apte and Nieder Korn, 1996). Although NK cells readily kill class I negative corneal endothelial cells *in vitro*, there is no evidence of NK cell-mediated injury to the corneal endothelium *in vivo*, even in conditions in which NK cells traffic through the eye. The absence of NK cell-mediated injury to the corneal endothelium *in vivo* is presumably the result of the inhibitory effects of the AH. At least two cytokines are present in the AH that independently suppress NK cell-mediated cytotoxicity: macrophage migration inhibitory factor (MIF) and TGF- β_2 (Rook *et al*, 1986; Apte and Nieder Korn, 1996; Apte *et al*, 1998). Thus, the absence of MHC class I determinants protects the corneal endothelium from injury inflicted by class I-restricted, CD8+ CTL, but concomitantly renders this cell layer potentially vulnerable to attack by NK cells that are programmed to kill any cell failing to express MHC class I antigens (Ciccone *et al*, 1994; Ljunggren *et al*, 1991). The buffering effects of the NK inhibitory factors in the AH counteract the vulnerability created by the absence of MHC class I antigens.

The innate immune apparatus also includes the complement system, which can inflict considerable injury to innocent bystander cells by recruiting and activating inflammatory cells such as neutrophils. Complement-related injury is minimized in the eye, however, by complement regulatory proteins that are found in the AH and vitreous (Lass *et al*, 1990; Goslings *et al*, 1998; Sohn *et al*, 2000). Corneal cells express complement regulatory proteins on their cell membranes, thereby providing additional protection against intraocular activation of the complement cascade (Bora *et al*, 1993; Lass *et al*, 1990). One theory holds that continuous low levels of complement activation are regular events in the eye, but injury to innocent bystander ocular cells is minimized by complement regulatory proteins in the AH and on the corneal cell membranes. This proposition is supported by studies in rats, which show that

in vivo administration of antibodies that block complement regulatory proteins results in severe uveitis (Sohn *et al*, 2000).

Cell Membrane-Bound Molecules That Promote Immune Privilege in the Eye The cells that line the interior of the eye also contribute to ocular immune privilege. The apoptosis-inducing cell membrane molecule, FasL (CD95L), is widely expressed on ocular cells and is effective in deleting inflammatory cells that enter the eye in response to various insults such as viral infections (Griffith *et al*, 1995). FasL on corneal cells augments the immune privilege of corneal allografts. That is, corneal allografts failing to express functional FasL are twice as likely to undergo immune rejection as are corneal grafts that display normal FasL (Stuart *et al*, 1997; Yamagami *et al*, 1997).

In addition to FasL, cells lining the AC are decorated with complement regulatory proteins (Lass *et al*, 1990; Bora *et al*, 1993; Sohn *et al*, 2000). The expression of complement decay-accelerating factor on the corneal epithelium appears to protect this cell layer of corneal allografts from cytolysis by complement-fixing alloantibody. Corneal epithelial cells from C57BL/6 mice are totally resistant to lysis by complement-fixing anti-C57BL/6 alloantiserum that is highly lytic for C57BL/6 lymphocytes (Hargrave *et al*, 2000; Hegde *et al*, 2002). By contrast, corneal endothelial cells are highly susceptible to lysis by complement-fixing alloantibody *in vitro*, but are not adversely affected *in vivo* because passive transfer of alloantibody does not culminate in corneal allograft rejection (Hegde *et al*, 2002). The endothelium of the corneal allograft is continuously bathed in the AH, which undoubtedly has a buffering effect due to the complement regulatory proteins that are constitutively present in the AH.

Classical class Ia MHC molecules are either feebly expressed or absent on many cells within the eye (Fujikawa *et al*, 1982; Bakker and Kijlstra, 1985; LeBouteiller, 1994; Nieder Korn *et al*, 1999; Treseler *et al*, 1984). According to the "missing self" hypothesis, the presence of classical class Ia MHC molecules is crucial for transmitting inhibitory signals to NK cells, which are programmed to kill MHC class I negative cells (Ljunggren *et al*, 1991). Thus, ocular cells failing to express adequate quantities of MHC class I molecules are potential targets for cytolysis by NK cells. However, murine ocular cells failing to express classical class Ia MHC molecules display significant expression of Qa-2 molecules (Nieder Korn *et al*, 1999). Qa-2 is a family of nonclassical, class Ib molecules that are closely associated with tolerance and are believed to exert anti-inflammatory effects. Moreover, nonclassical class Ib MHC molecules are capable of sending "off signals" to NK cells. The latter property has important implications in protecting ocular cells that fail to express classical class Ia MHC molecules and are not bathed by AH.

WHAT IS THE RAISON D'ÊTRE OF OCULAR IMMUNE PRIVILEGE AND WHAT HAPPENS WHEN PRIVILEGE IS LOST?

The eye is an extension of the brain, both embryologically and anatomically, and possesses the remarkable neurological complexity of the central nervous system. Like other elements of the central nervous system, many ocular cells cannot regenerate if injured by trauma or inflammation. Dampening potentially injurious inflammatory responses in the eye has obvious benefit for protecting such ocular tissues from irreparable damage. Accordingly, it is not surprising that multiple mechanisms contribute to ocular immune privilege (**Table 1; Fig 1**). Like any homeostatic mechanism, however, immune privilege has its limitations.

When ocular immune privilege breaks down, the consequences can be blinding. It is noteworthy that the leading causes

Table 1. Factors that Support Immune Privilege in the Eye

Effect on Immune Privilege	Factor	Location
Inhibition of T cell proliferation	TGF- β_2	Aqueous humor
	VIP	Aqueous humor
	Müller cells	Retina
	Pigmented retinal epithelial cells	Retina
Inhibition of DTH	ACAID	Anterior chamber, vitreous, subretinal space
	TGF- β_2	Aqueous humor
	VIP	Aqueous humor
	CGRP	Aqueous humor
	α -MSH	Aqueous humor
Deletion of infiltrating inflammatory cells	FasL	Cornea, iris, retina, ciliary body
Inhibition of NK cells	MIF	AH, lens, cornea
	TGF- β_2	AH
	Qa-2?	Cornea, iris, retina, ciliary body
Inhibition of complement	membrane-regulatory bound	Cornea, ciliary body, iris, choroid
	soluble complement	Aqueous humor
	regulatory proteins	

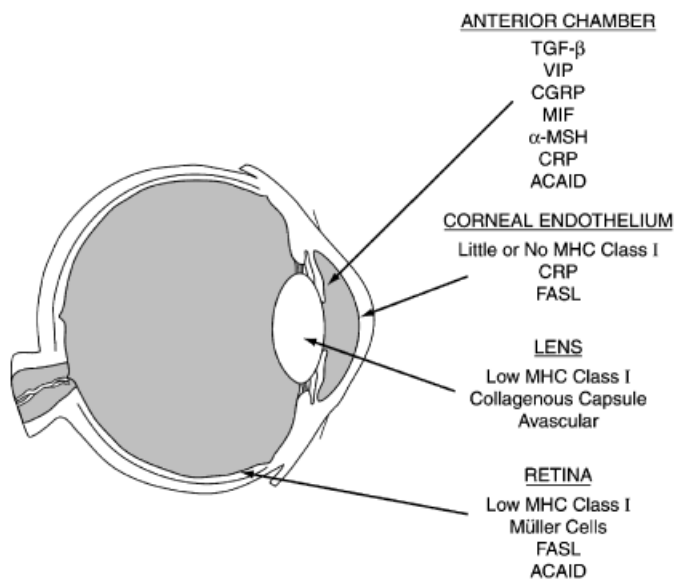


Figure 1. Immune privilege in the eye involves multiple mechanisms and factors: α -MSH (α -melanocyte-stimulating hormone), ACAID (anterior chamber-associated immune deviation), CGRP (calcitonin gene-related protein), CRP (complement regulatory proteins), MIF (macrophage migration inhibitory factor), TGF- β transforming growth factor- β , vasoactive active intestinal peptide.

of infectious blindness are immune mediated. The nematode *Onchocerca volvulus* affects over 17 million people and accounts for over 250,000 cases of corneal blindness (Pearlman, 1997). Between 6 and 9 million people are blind because of trachoma, a chlamydial infection of the cornea (Taylor and Bell, 1991). In the United States, herpes simplex virus produces keratitis in 20,000 people each year and is the leading cause of infectious blindness in North

America (Liesegang *et al*, 1989). The blindness produced by each of these infectious diseases is immune mediated (Pearlman, 1997; Streilein *et al*, 1997; Niederkorn, 2002). In each case, an overexuberant TH1- or TH2-mediated inflammatory response to the ocular pathogen results in extensive collateral damage to innocent bystander cells in the eye. In ridding the eye of the pathogen, the immune system unwittingly inflicts irreparable damage to ocular tissues that are incapable of regeneration. The teleological argument might be made that ocular immune privilege yields to pathogens that are potentially life threatening and releases the immune system to protect the host, even at the risk of blindness.

The blinding effect of autoimmune diseases of the eye is further evidence of the importance of ocular immune privilege. Autoimmune responses to retinal and uveal antigens produce inflammation of the uveal tract and are significant causes of visual loss in humans and animals. Results from animal studies have shown that antigens present in the retina and uveal tract are potentially immunogenic if combined with potent adjuvants and introduced outside of the eye. The resulting inflammatory eye disease, called experimental autoimmune uveitis (EAU), has been a model for studying the pathogenesis and immunobiology of a variety of naturally occurring inflammatory eye diseases. The relatively rare incidence of uveitis in the human population, however, and the exceptional manipulations that are needed for inducing EAU in animals support the notion that ocular immune privilege is an effective mechanism for protecting the eye against immune-mediated injury provoked by ocular autoantigens.

Immune Privilege of the Hair Follicle Billingham and Silvers were the first to suggest that the epithelial hair bulb was endowed with immune privilege (Billingham and Silvers, 1971). Their conclusion was based on observations with skin allografts exchanged between pigmented donors and albino recipients. The skin grafts from black guinea pig donors became depigmented and were presumed to have been rejected; however, the subsequent emergence of black hair shafts in the graft bed indicated that at least some of the donor melanocytes had escaped immune rejection and had survived in the hosts' hair bulbs. It was concluded that the hosts' hair shafts had offered the donor melanocytes sanctuary from immunological attack. In the 30 years since the seminal observations of Silvers and Billingham, the immune privilege of the hair follicle has garnered only limited interest from the dermatological and immunological research communities (Paus *et al*, 1999).

The immunological architecture of the hair follicle provides clues for explaining its immune privilege. The growth stage of the hair follicle, anagen, is characterized by a conspicuous absence of class Ia MHC antigens in the proximal hair follicle epithelium (Westgate *et al*, 1991; Christoph *et al*, 2000; Paus *et al*, 1999). Cells of the immune system are also sparsely distributed in the hair follicle. The entire lower two-thirds of the anagen hair follicle is devoid of antigen-presenting Langerhans cells (LC) (Moresi and Horn, 1997; Paus *et al*, 1999). Only scant numbers of NK cells, CD4+ T cells, and CD8+ T cells are found in the lower portions of the proximal hair follicle and bulb (Christoph *et al*, 2000).

A number of studies have demonstrated the effect of hair cycle on the immunobiology of the skin (Claesson and Hardt, 1970; Hoffman *et al*, 1996; Tokura *et al*, 1997). Contact hypersensitivity (CHS) is inhibited when haptens are administered to skin in which all of the hair follicles are synchronized in telogen (Hofmann *et al*, 1998). The hyporesponsiveness to haptens has been attributed to the local production of immunosuppressive factors, such as TGF- β (Gruschwitz *et al*, 1990; Schmid *et al*, 1996) and adrenocorticotrophic hormone (Slominski *et al*, 1993), that are elaborated in anagen hair follicles.

Although there are some similarities in the mechanisms of immune privilege of the hair follicle and eye, there are noteworthy differences. FasL is believed to contribute to the immune privilege of the eye, but is absent from the hair follicle

(Christoph *et al*, 2000). ACAID plays a major role in sustaining immune privilege in the eye; however, the possibility that an ACAID-like phenomenon occurs in the hair follicle has not been addressed to date. It is not known if NK cells and other components of the innate immune apparatus are restrained in the hair follicle as they are in the eye.

If the anagen hair bulb is an immune-privileged site, what is the adaptive advantage of having an "immunological blind spot" in an organ that serves as a major barrier to a panoply of environmental pathogens? It has been suggested that follicular immune privilege might function to prevent potential auto-antigens in the skin from provoking deleterious autoimmune responses (Paus *et al*, 1999). One wonders if the putative location of keratinocyte stem cells in the "bulge" area of the hair follicle not only shields these crucial cells from environmental factors but also protects them from immune-mediated injury. Although there are many intriguing questions that beg to be addressed, the original observation by Billingham and Silvers demonstrating that the hair follicle provides sanctuary to allogeneic melanocytes is still as provocative today as it was three decades ago and hints that immune privilege of the hair follicle has yet to reveal all of its secrets (Billingham and Silvers, 1971).

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